CLAIMS:

1. A method for identifying nucleic acid ligands of a target molecule from a candidate mixture of nucleic acids, said method comprising:

a) preparing a candidate mixture of nucleic acids, said nucleic acids containing photoreactive groups;

b) contacting said candidate mixture with said target molecule, wherein nucleic acid sequences having increased affinity to the target molecule relative to the candidate mixture form nucleic acid-target molecule complexes;

c) irradiating said candidate mixture, wherein said nucleic acid-target molecule complexes photocrosslink;

d) partitioning the crosslinked nucleic acid-target molecule complexes from free nucleic acids in the candidate mixture; and

e) identifying the nucleic acid sequences that photocrosslinked to the target molecule.

2. The method of claim 1 further comprising the step:

f) repeating steps b) through d); and

g) amplifying the nucleic acids that photocrosslinked to the target molecule to yield a mixture of nucleic acids enriched in sequences that are capable of photocrosslinking the target molecule.

3. The method of claim 1 wherein said photoreactive groups are selected from the group consisting of 5-bromouracil, 5-iodouracil, 5-bromovinyluracil, 5-iodovinyluracil, 5-azidouracil, 4-thiouracil, 5-bromocytosine, 5-iodocytosine, 5-bromovinylcytosine, 5-iodovinylcytosine, 5-azidocytosine,

8-azidoadenine, 8-bromoadenine, 8-iodoadenine, 8-azidoguanine, 8-bromoguanine, 8-iodoguanine, 8-azidohypoxanthine, 8-bromohypoxanthine, 8-iodohypoxanthine, 8-azidoxanthine, 8-bromoxanthine, 8-iodoxanthine, 5-bromodeoxyuracil, 8-bromo-2'-deoxyadenine, 5-iodo-2'-deoxyuracil, 5-iodo-2'-deoxycytosine, 5-[(4-azidophenacyl)thio]cytosine, 5-[(4-azidophenacyl)thio]uracil, 7-deaza-7-iodoadenine, 7-deaza-7-iodoguanine, 7-deaza-7-bromoadenine, and 7-deaza-7-bromoguanine.

4. The method of claim 1 wherein said target molecule is a protein and removal of the target protein from the nucleic acid-target molecule complex is achieved by proteolytic digestion.

5. The method of claim 1 wherein said nucleic acid ligand is capable of modifying the biological activity of said target molecule.

6. A method for identifying photocrosslinking nucleic acid ligands of a target molecule from a candidate mixture of nucleic acids, said method comprising:

a) preparing a candidate mixture of nucleic acids;

b) contacting said candidate mixture with said target molecule, wherein nucleic acid sequences having increased affinity to the target molecule relative to the candidate mixture form nucleic acid-target molecule complexes;

c) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture; and

d) amplifying the increased affinity nucleic acids to yield a ligand-enriched mixture of nucleic

acids, whereby nucleic acid ligands of the target molecule may be identified;

e) incorporating photoreactive groups into said increased affinity nucleic acids;

f) repeating step b)

g) irradiating said increased affinity nucleic acids, wherein said nucleic acid-target molecule complexes photocrosslink;

h) repeating step d) and e).

7. A method for identifying a disease comprising producing a nucleic acid ligand by the method of claim 1 to a target molecule specifically associated with said disease.

8. A method of treating a disease comprising:

a) identifying a nucleic acid ligand to a target molecule associated with a disease through the method of claim 1;

b) introducing a nucleic acid ligand in a patient;

c) administering photoreactive molecules wherein said expressed nucleic acid ligand contains photoreactive groups; and

d) irradiating said patient, wherein said nucleic acid ligand crosslinks a target molecule.

9. A method for identifying nucleic acid ligands able to crosslink a target molecule comprising the method of claim 1 followed by steps b) through d) of claim 6.

10. The method of claim 6 wherein step a) is conducted with a candidate mixture of nucleic acids containing photoreactive groups.

11. Nucleic acid ligands able to crosslink the target molecule produced by the method of claim 1 comprising one or more photoreactive groups.

12. The nucleic acid ligands of claim 11 further comprising one or more of the photoreactive groups selected from the group set forth in claim 3.

13. Nucleic acid ligands able to crosslink the target molecule produced by the method of claim 6 comprising one or more photoreactive groups.

14. The nucleic acid ligands of claim 13 further comprising one or more of the photoreactive groups selected from the group set forth in claim 3.

15. Nucleic acid ligands able to crosslink the target molecule produced by the method of claim 9 comprising one or more photoreactive groups.

16. The nucleic acid ligands of claim 15 further comprising one or more of the photoreactive groups selected from the group set forth in claim 3.

17. A method for identifying nucleic acid ligands from a candidate mixture of nucleic acids, said nucleic acid ligands being a ligand of a given target molecule comprising:

a) preparing a candidate mixture of nucleic acids;

b) contacting said candidate mixture with the target molecule, wherein nucleic acids having increased affinity to the target molecule form nucleic acid-target complexes;

c) partitioning the increased affinity nucleic

acids from the remainder of the candidate mixture, said partitioning step resulting in two differentiable nucleic acid pools; and

d) amplifying the increased affinity nucleic acids to yield a ligand-enriched mixture of nucleic acids.

18. The method of claim 17 wherein step c) consists of

(i) a first cDNA extension with a nucleic acid polymerase such that full length cDNA is not obtained from said increased affinity nucleic acids forming nucleic acid-target complexes;,

(ii) removal of the target molecule; and

(iii) a second cDNA extension with a nucleic acid polymerase, wherein cDNA is synthesized from said increased affinity nucleic acids.

19. The method of claim 18, wherein said nucleic acid polymerase is selected from the group consisting of DNA polymerase, RNA polymerase, reverse transcriptase, and Qβ-replicase.

20. The method of ~~claim 18,~~ wherein said first cDNA extension step is performed in the presence of chain terminating nucleotide triphosphates and said second cDNA extension step is performed in the absence of chain terminating nucleotide triphosphates, wherein only the cDNA product from the increased affinity oligonucleotide is amplifiable by PCR.

21. The method of claim 18, wherein said first cDNA extension step is performed in the presence of four dNTPs, followed by removal of said target, and said second cDNA extension step is performed in the presence

of modified nucleotides resistant to enzymatic cleavage by restriction enzymes, single- or double-stranded nucleases, or uracil DNA glycosylase, and incubation of the cDNA products with a nuclease enzyme.

22. The method of claim 18, wherein said first cDNA extension step is performed in the presence of modified nucleotides that allow retention of the cDNA product on an affinity matrix, and said second cDNA extension step is performed in the presence of the four dNTPs, wherein cDNA synthesized from free or low affinity oligonucleotides is removed by retention on an affinity matrix.

23. The method of claim 18, wherein said first cDNA extension step is performed in the presence of four dNTPS, and said second cDNA extension step is performed in the presence of modified nucleotides that allow retention of the cDNA product on an affinity matrix, wherein cDNA synthesized from increased affinity oligonucleotides is removed by retention on an affinity matrix.

24. A method for identifying nucleic acid ligands from a candidate mixture of nucleic acids, said nucleic acid ligands being a ligand of a given target molecule comprising:

a) preparing a candidate mixture of nucleic acids;

b) contacting said candidate mixture with the target molecule, wherein nucleic acids having increased affinity to the target molecule form nucleic acid-target complexes;

c) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture, said

partitioning step comprising

(i) a first cDNA extension with a nucleic acid polymerase in the presence of dNTPs sensitive to chemical cleavage;

(ii) removal of the target molecule;

(iii) a second cDNA extension with a nucleic acid polymerase in the presence of modified nucleotides resistant to chemical cleavage;

(iv) incubation of said first and second cDNA extension products with a nucleotide degrading chemical; and

d) amplifying the increased affinity nucleic acids to yield a ligand-enriched mixture of nucleic acids.

25. A method to isolate single-stranded nucleic acids comprising

a) preparing a candidate mixture of nucleic acids;

b) contacting said candidate mixture with the target molecule, wherein nucleic acids having increased affinity to the target molecule form nucleic acid-target complexes;

c) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture, said partitioning step including primer extension inhibition wherein two differentiable cDNA pools are generated; and

d) amplifying the increased affinity nucleic acids comprising

(i) amplifying the increased affinity nucleic acid ligands with a 5' PCR primer, wherein a ligand-enriched mixture of truncated, double-stranded nucleic acids is produced;

(ii) asymmetric amplification of the truncated, double-stranded nucleic acids with a

second 5' primer, wherein a ligand-enriched elongated, single-stranded nucleic acid mixture is produced.

26. A method for identifying double-stranded nucleic acid ligands from a candidate mixture of nucleic acids, said nucleic acid ligands being a ligand of a given target molecule comprising:

a) preparing a candidate mixture of nucleic acids;

b) contacting said candidate mixture with the target molecule, wherein nucleic acids having increased affinity to the target molecule form nucleic acid-target complexes;

c) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture, said partitioning step comprising

(i) incubating with exonuclease enzyme wherein full length double-stranded nucleic acids not forming nucleic acid-target complexes are degraded and double-stranded nucleic acids forming nucleic acid-target complexes are partially protected from degradation;

(ii) removing said exonuclease enzyme and said target;

(iii) extending said double-stranded nucleic acids with polymerase, wherein double-stranded nucleic acid ligand-enriched candidate mixture is regenerated.

27. A method for identifying nucleic acids with catalytic activity from a candidate mixture of nucleic acids, comprising:

a) preparing a candidate mixture of nucleic acids;

b) contacting said candidate mixture with the target molecule, wherein nucleic acids having increased affinity to the target molecule form nucleic acid-target complexes;

c) partitioning the increased affinity nucleic acids from the remainder of the candidate mixture, said partitioning step comprising

(i) annealing an extension primer to the extreme 5' end of said nucleic acids;

(ii) performing a cDNA extension; and

d) amplifying the full length cDNA to yield a second mixture of nucleic acids enriched for catalytic nucleic acids.

28. An automated method of identifying nucleic acid ligands comprising the method of claim 17 wherein said nucleic acids are covalently attached to an affinity column and said increased affinity nucleic acids are reattached to the affinity column, wherein all steps are performed in a single reaction vessel.